REMARKS

1. Overview

The last office action indicated that claims 90-93, 95, 96, 100 and 109 were allowed. Certain other claims were rejected under 35 USC 112, but deemed to distinguish the prior art. Thus, claims 90-93, 95-96, 100 and 109 were deemed allowable over the prior art and claims 87, 101, 103 and 108 were deemed allowable over the prior art if rewritten to avoid dependency on a rejected base claim. Only claims 12, 18, 19, 75, 102, 104-107 were rejected over prior art (OA §16-19).

Claims 12, 18-19, 75, 83, 97-99, 102, 104-7 were rejected on written description (OA §9-12) and enablement (OA §13-15) grounds. There was also a separate description rejection of claims 105-7 (OA §8). Finally, the Examiner questioned the definiteness of language in claims 12, 102, 97-99 (OA §5-6), and the relationship of 104 to 83 (OA §20).

Claims 12, 90, 97-99, 109 have been amended, claim 102, 103, 106, 107 and 109 have been cancelled, and claims 110-111 have been added.

We thank Examiner Ramirez and Examiner Prouty for according us a telephonic interview to discuss this case.

Claim 12 has been amended to (1) incorporate the (b1)-(b3) limitations of old claim 110, (2) to change the required % identity from 99% to the previously suggested value of 95%, and (3) to delete the immunological activity limitation.

The Examiner agreed that amendment (1) is sufficient to overcome the prior art rejection of claim 12. The 99% limitation was therefore no longer needed for that purpose, but an overall % identity limitation was retained, albeit in the less stringent form, to satisfy description/enablement concerns. The Examiners accepted that a polypeptide of claim 12, with proteolytic activity per limitation (i), satisfied 35 USC 112, but expressed concern as to utility, etc. if the polypeptide's activity were

purely immunological. In order to put claim 12 into condition for allowance, we deleted the alternative immunological activity limitation (ii). The immunological activity limitation was also deleted from claims 97-99.

Claim 90, clause (1)(i), has been amended for consistency with the proteolytic activity limitation as previously presented and accepted in, e.g., claim 12. We have also amended it to delete activity limitation (iii), which was previously deleted from the other independent claims.

New claim 110 recites a polypeptide which differs from mature PAPP-A2 by not more than 16 insertions and/or deletions and/or substitutions. Mature PAPP-A2 is 1558 a.a., and 1% of 1558 is 16.

New claim 111 recites a polypeptide which is at least 99% identical to mature PAPP-A2, and "consists of 1548-1568 amino acids". Thus it allows subtracting or adding up to ten amino acids to mature PAPP-A2.

2. Prior Art Issues

In response to OA §16-19, claim 12, as amended, is not anticipated by Farr et al. The Farr 1624 a.a. polypeptide differs from the polypeptide of claim 12(a) by three nonconservative substitutions (G/E, I/T, L/P), one conservative substitution (D/D), and addition of residues 168-233 of SEQ ID NO:2. Claim 12(b) does not allow nonconservative substitutions, see (b3), and the addition exceeds that allowed by (b1).

The Farr 1542 a.a. polypeptide differs from the polypeptide of 12(a) by the same substitutions, and deletion of residues 234-249 of SEQ ID NO:2. It therefore violates 12(b1) and 12(b3).

3. Non-Art Issues

3.1. In response to OA §5, claim 12 is amended to recite "from the polypeptide of (a)" in place of "therefrom", as

suggested by the Examiner. Claim 102 has been cancelled.

3.2. In response to OA §6, claims 97-99 are amended to identify the fragment as being "of said polypeptide", and to make clearly that "said polypeptide or cleavable fragment" must comprise sequence (II), as suggested by the examiner.

3.3. In response to OA §7, rejecting claims 105-7, claims 106-107 are cancelled. With respect to claim 105, we believe that the disclosed embodiments, featuring deletion of "1-10" amino acids, and of "2-5" amino acids, provide support for limitation of 1-5, i.e., deletion of 1 amino acid is a sub-embodiment of "1-10", and can be combined with 2-5 to yield 1-5. Indeed, we believe that a person skilled in the art would consider "2-5" to be a typo, and "1-5" intended, since deletion of "1-10" is taught, deletion of one amino acid is a smaller perturbation than that of "2-5", and <u>insertion</u> of "1-5" is taught.

However, we would agree, if need be, to an E.A. to change "1 to 5" to "2 to 5".

3.4. In response to OA §20, claim 104 has been cancelled.

3.5. Claims 12, 18-19, 75, 83, 97-99, 102, 104-7 were rejected for allegedly failing to comply with the written description requirement. In the interview, the Examiners stated that their concern with claims 12, 97-99 and 102 was with respect to coverage of variants which lacked proteolytic activity (note the "and/or" in claims 12 and 97-99). This was consistent with the fact that claim 103, which limited 102 to require proteolytic activity, was <u>not</u> included in this written description rejection.

3.5.1. We have now amended claims 12 and 97-99 so that "proteolytic activity" is mandatory, and it is our understanding that this overcomes this rejection of claims 12, 97-99 and dependent claims 18-19, 75, 83 and 105. Claims 102, 104-7 have been cancelled.

3.5.2. In the interest of providing a complete prosecution

record, we would like to comment on one argument made in the office action even though it no longer seemed to trouble the Examiners.

Page 6 of the office action suggested that the allowed sequence divergence (then 1%) could fortuitously result in an additional, undisclosed biological function. Whether or not that be the case, that additional function is legally irrelevant. The specification need only disclose one utility for the claimed polypeptides. It is improper for the PTO to speculate that the polypeptides could fortuitously possess additional functions and then fault applicant for not fully disclosing them. The Written Description Training Materials plainly contemplate that a polypeptide of known sequence is "representative" of the genus defined by all polypeptides at least 95% identical to the original one, and retaining the original enzymatic activity. That 5% divergence could result in the mutant being able to attach a new substrate (i.e., possess an additional function), but the WDTM don't see this as a problem.

While a divergence of 1% or 5%, in certain locations, might result in loss of the anti-IGFPB-5 activity of PAPP-A2, such mutants fall outside of claim 12 by virtue of its activity limitation.

3.6. Claims 12, 18-19, 75, 83, 97-99, 102, 104-7 were also rejected for alleged lack of enablement of their full scope. The Examiner argues on bottom of page 9 that those polypeptides which lack enzymatic activity do not have patentable activity "since being able to be detected by an antibody is not considered to be a specific utility". In the interview, we were advised that limitation of claims 12 and 97-99 to require proteolytic activity would overcome this rejection.

3.7. We wish to note for the record that the PTO has allowed claim 90, even though it does cover non-proteolytic polypeptides. We believe that the PTO recognized that claim 90

(unlike claims 12 and 97-99 as examined) does not permit amino acid substitutions. See the discussion of antibody recognition of sequence variants in the final paragraph of OA page 10. Claim 90 only covers mature PAPP-A2, certain fragments of mature PAPP-A2, and certain related fusion proteins.

Indeed, the Examiner acknowledged "that if patentable utility is found for a polypeptide, a fragment of said polypeptide would have utility as an antigen" (OA, page 10, first full paragraph). Mature PAPP-A2 has utility, as a proteolytic agent, so fragments of mature PAPP-A2 seemingly have utility. Moreover, as a 1558 a.a. polypeptide, it quite clearly will elicit an immune response if suitably administered.

We wish to make it quite clear that we consider the immunological utility recited in claim 90 to be a "specific utility".

The Revised Interim Utility Guidelines Training Materials said that a specific utility is "a utility that is specific to the subject matter claimed", as contrasted with "a general utility that would be applicable to the broad class of the invention". It explained that the disclosure of the utility of a polypeptide as being that of a "gene probe" or a "chromosome marker", when **"in the absence of disclosure of a specific DNA target"**, would be "general".

Here, the immunological activity is a binding utility with a specific target (an antibody which recognizes mature PAPP-A2) and hence is a specific utility. It is not a property possessed by all or even most polypeptides.

It thus appears that claim 90 correctly was not rejected under 35 USC 112 even though it covers non-proteolytic yet immunologically active fragments of mature PAPP-A2.

On page 10, first full paragraph, the Examiner raises the issue of whether a "variant" of an antigen still possesses specific utility as an antigen. The Examiner's stated concern

is that the mutations could destroy epitopes. If so, then the issue is not that the asserted utility is non-specific, but rather whether it is not enabled. We don't need to analyze this issue, as claim 90 does not cover variants.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By: _____
Iver P. Cooper
Reg. No. 28,005

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
G:\ipc\g-i\hoib\Oxvig1A\PTO AMENDMENT2.WPD